Current Review

Lithium and hematopoiesis

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Some of lithium's effects on blood cell formation suggest that the element may be of value in treating hematologic disorders. Lithium enhances granulopoiesis and thereby induces neutrophilia. Two possible mechanisms of action are suggested: a direct action on the pluripotent stem cells, or an inhibition of the suppressor cells (thymus-dependent lymphocytes) that limit hematopoiesis. Lithium also inhibits erythropoiesis. Although most studies use concentrations at or above pharmacologic levels there is evidence that lithium plays a role in normal cell metabolism.

Certains des effets du lithium sur la formation des cellules sanguines laissent supposer que cet élément pourrait être utile dans le traitement de maladies hématologiques. Le lithium augmente la granulopoïèse et, de la sorte, provoque une neutrophilie. Deux mécanismes d'action possibles sont proposés: une action directe sur les cellules souches pluripotentes ou une inhibition des cellules de suppression (lymphocytes thymodépendants) qui limitent l'hématopoïèse. Le lithium inhibe également l'érythropoïèse. Bien que la plupart des études aient utilisé des concentrations égales ou supérieures aux niveaux pharmacologiques, il apparaît que le lithium joue un rôle dans le métabolisme cellulaire normal.

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The biologic and pharmacologic effects of lithium were reviewed exhaustively 25 years ago.[1] Since then this element's influence on leukopoiesis has been studied in detail.[2,3] Therapeutic use of lithium salts is associated with neutrophilia, which reflects an expansion of the total blood granulocyte pool through increased production in the bone marrow.[4] Lithium salts may also cause an increase in eosinophil and platelet counts,[5,6] although this has not been a uniform finding.[7] There does not appear to be any change in hemoglobin concentration, hematocrit or reticulocyte counts in the peripheral blood, but lithium salts do produce lymphocytopenia,[5,7] a phenomenon that demands further investigation.

Therapeutic use of lithium in hematologic disorders

In light of lithium's effects on granulopoiesis in humans, it was predictable that lithium compounds would be administered to patients with hematologic disorders. However, although it was given to several individuals with aplastic anemia, lithium has been reported to produce clear amelioration of pancytopenia only once.[8] In the canine version of another stem cell disease, cyclic hematopoiesis (formerly called cyclic neutropenia), lithium restored the numbers of circulating blood cells to nearly normal.[9] Anecdotal experience in humans has been less encouraging.[5] Perhaps the most promising use of lithium, which is supported by the results of clinical trials, will be in blocking the neutropenia induced by chemotherapeutic agents given to cancer patients.[10] However, such use of lithium is not without hazard. In healthy volunteers lithium carbonate reduced the bactericidal capacity of neutrophils and the responsiveness of lymphocytes to antigens.[11] An earlier suggestion that lithium therapy may increase the frequency of chromosome breaks[12] was not confirmed by subsequent investigation in vitro[13] and ex vivo.[14,15]

Pharmacologic effects on hematopoiesis in humans

Lithium stimulates the formation of granulocyte–macrophage colonies in human bone marrow, both in vitro[16] and in vivo.[5] The effect in vitro is evidently concentration-dependent. At concentrations of lithium close to the therapeutic range in plasma, the formation of granulocyte–macrophage colonies is stimulated, while at concentrations associated with clinical toxicity, granulopoiesis in vitro is inhibited.[16-19] Despite this in vitro relationship, however, granulocytopenia has not been described in association with lithium poisoning.[20] It is unfortunate that many of the studies published do not clearly state the final concentration of the salt that was used or even the nature of the compound.[21] In contrast to the effects on granulopoiesis, pharmacologic concentrations of lithium inhibit the generation of erythrocytes from human bone marrow in vitro.[17]

In the pathogenesis of lithium-induced neutrophilia there may be significance in the relation of lithium administration to changes in plasma cortisol levels. Lithium and cortisol have many effects in common (Table I). The results of two studies in patients with psychiatric diseases indicated that lithium therapy was accompanied by an increase in the levels of plasma cortisol.[22,23] A more careful study by others, however, revealed that the therapeutic use of lithium was not associated with changes in adrenocortical function.[24] The reason for these differing results may be that the patients in the first two studies were in clinical relapse, while those in the third were in clinical remission; the latter group was also receiving a lower dose of lithium carbonate. Volunteers without psychiatric diseases who were given lithium in therapeutic doses showed a reduction in their morning levels of plasma cortisol in one study[25] but no changes in another.[6] Whatever influence lithium may have on plasma cortisol concentrations is still unsettled, but it seems that it may be affected considerably by the clinical status of the recipients.

Hematopoietic cell targets and mechanisms of action of lithium

The evidence suggests that lithium can modulate human hematopoiesis. This effect may be mediated through different routes (Fig. 1). The unique clinical experience in aplastic anemia and the studies of canine cyclic hematopoiesis suggest a direct action on the pluripotent stem cell.[26] This possibility is supported by the observed stimulation of murine spleen colony-forming cells in vivo and in vitro.[27-29] However, the hematologic responses of mice and humans to cationic modulation may not be the same.[30,31]

An alternative mechanism can be based on the lithium-induced inhibition of suppressor cells, which are the thymus-dependent lymphocytes (T cells) that limit hematopoiesis.[32,33] In humans therapeutic concentrations of lithium apparently inhibit the suppressor lymphocytes by reducing the activity of adenosine 3′,5′-cyclic monophosphate (cyclic AMP).[34] In contrast, lithium stimulates the responsiveness of lymphocytes to the mitogen phytohemagglutinin.[35] Prostaglandin E (PGE), however, has the opposite effect on mitogen responsiveness,[36] and PGE_2 selectively increases the activity of cyclic AMP in the suppressor lymphocytes of humans.[37] Thus, in humans lithium and PGE produce opposing effects on the same target cells via the same pathway, and these effects are manifest in hematopoiesis by the bone marrow in vitro.[17] In addition, the two substances produce contrasting effects on granulopoiesis and erythropoiesis: lithium stimulates the former and inhibits the latter, whereas PGE does the opposite.[17,38] No explanation for this difference is yet apparent, but, like colony-stimulating factor, PGE and erythropoietin are products of human monocytes.[39,40]

The stimulation of granulopoiesis by lithium does not appear to be due to either a direct effect on the committed granulocyte–macrophage progenitor cells or a direct promotion of synthesis or release of colony-stimulating factor from monocytes.[17,18] Lithium probably enhances the elaboration of colony-stimulating factor by monocytes through inhibition of the suppressor cells.[41,42]

Studies of lithium's effect on the generation of T-cell colonies[43] and immunoglobulins[44] from the peripheral blood lymphocytes of humans have used concentrates of whole mononuclear cells, thus failing to take into account lithium-induced lymphocytopenia and altered T cell–monocyte interactions. Furthermore, one recent description of the kinetics of lithium-stimulated granulopoiesis[45] can be interpreted entirely on the basis of spontaneous cell death and differences in solute diffusion.

Physical chemistry and cell membrane transport

Although the physical and chemical similarities of sodium, potassium and lithium have led to their place-

Table I—Actions of lithium and cortisol on blood cells and hematopoiesis in humans and animals

Action	Lithium	Cortisol
Increase in total blood granulocyte pool	+	+
Lymphocytopenia	+	+
Inhibition of suppressor T cells	+	+
Low-dose stimulation of granulocyte–macrophage progenitor cells	+	+
High-dose inhibition of granulocyte–macrophage progenitor cells	+	+
Inhibition of primitive erythroid progenitor cells	+	+
Increase in number of circulating granulocyte–macrophage progenitor cells	–	+
Stimulation of murine multipotent stem cells	+	+

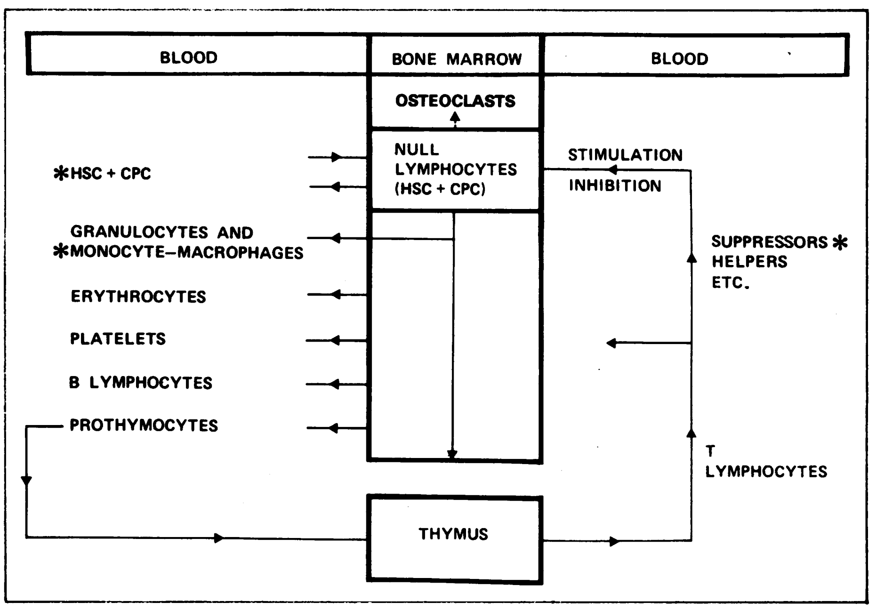

FIG. 1—Model of hematopoiesis with "null" (non-T, non-B) lymphocytes as source of blood cell precursors, which are subject to regulation by T lymphocytes.[32,33] HSC = hematopoietic stem cells; CPC = committed progenitor cells. Cellular targets for lithium indicated by asterisks.

ment in group 1A of the periodic table, these elements are physiologically quite distinct. Sodium is the major extracellular cation, potassium predominates within cells, and lithium exists in approximately equal concentrations in intracellular and extracellular fluids. Lithium may compete with divalent cations in tissue fluids, which might reflect the comparable charge densities of lithium and calcium and the similar ionic radii of lithium and magnesium.[46] The resemblance of lithium to calcium as ions could explain lithium's inhibition of erythropoiesis.[47] Likewise, the role of magnesium in cell proliferation[48] may be weakened in the presence of lithium. Since it appears likely that cations modulate the expression of genes,[49] membrane cation transport and the cationic control of proliferation in mammalian lymphocytes have become objects of considerable attention.[50-52]

The formation of blood cells is evidently subject to neural regulation,[53] so lithium's impact on neurotransmission is also likely to be relevant to hematopoiesis. In the neuromuscular apparatus lithium reduces the release of neurotransmitters[54] and the number of available acetylcholine receptors.[55] Choline is known to accumulate in erythrocytes after prolonged exposure to lithium,[56] and it may be converted to acetylcholine,[57] which can stimulate hematopoiesis.[58] In humans acetylcholinesterase in skeletal muscle is similar if not identical to the enzyme in erythrocytes,[59] and it has been identified in T lymphocytes.[60] It is also secreted by the megakaryocytes of mice,[61] but the bone marrow acetylcholinesterase of humans is found predominantly in erythroid cells.[62] While no clear links can yet be shown between these various phenomena, they do suggest that lithium may influence the neural regulation of hematopoiesis, and that lithium's mechanism of action in modifying the metabolism of nerves may be similar to its influence on blood cell formation. Nevertheless, lithium inhibits erythropoiesis in mice both in vitro and in vivo.[63]

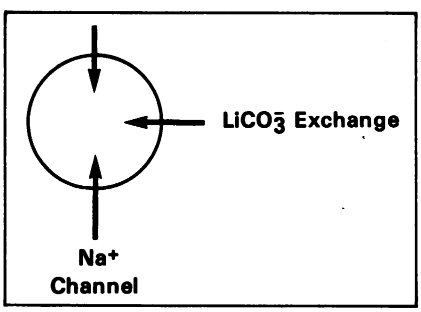

FIG. 2—Routes by which lithium crosses cell membranes.

Three main mechanisms move lithium across erythrocyte membranes.[64,65] Leakage is the major route of influx and has no known inhibitors. Efflux is accomplished largely by countertransport with sodium; it is inhibited by phloretin but not by ouabain, a steroid that specifically blocks the sodium–potassium pump. The exchange of lithium carbonate anions is the third route. It is bidirectional and is inhibited by dipyridamole and furosemide. An additional pathway, the sodium channel, admits lithium into excitable cells (Fig. 2). This route is opened by veratradine and closed by tetrodotoxin. The subsequent intracellular fate of lithium is unknown, but it may have an effect on processes mediated by cyclic AMP and regulated by polypeptide hormones.[66] The recent description of a lithium ionophore, which induces permeability to alkali metal cations in biologic membranes, may provide further insight in this area.[67]

Lithium and normal physiology

Almost all in-vitro studies of lithium's influence on hematopoiesis have dealt with concentrations at and much above pharmacologic levels. Although the element is concentrated in bone in cases of fatal poisoning,[68] there are no reliable data on lithium's concentration in normal human tissues. This is hardly surprising since the lower limit of detection by conventional atomic absorption spectrophotometry is of the order of $10^{-5}M$. Using tissue culture techniques, however, one of us (R.D.B.) has found that granulopoiesis in normal human bone marrow can be stimulated by as little as 1.5×10^{-9} *M* lithium. This phenomenon also occurs with two other group 1A elements, rubidium and cesium. Unlike sodium and potassium, none of these monovalent cations is currently used in tissue culture media. The findings, though, suggest that lithium, like other trace metals,[69] may make a physiologic contribution to hematopoiesis.

Conclusions

Hematopoiesis can evidently be influenced by the administration of lithium salts, and this has led to comparison with the action of cortisol. Lithium enhances granulopoiesis, both in vivo and in vitro, and inhibits erythropoiesis. Some clinical experience suggests that lithium may well be therapeutic in disorders of blood cell formation. It seems that the lithium ion may have an impact on both proliferation and differentiation, as predicted by a model in which interacting lymphocyte subpopulations have a central role in hematopoiesis. A number of possible cell targets have been identified. Recent experiments and our knowledge of the physical chemistry of cations and membrane transport also suggest that lithium does have a role in normal cell metabolism.

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This list is an acknowledgement of books received. It does not preclude review at a later date.

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